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EDITORIAL COMMENTARY

Optimizing efavirenz treatment: *CYP2B6* genotyping or therapeutic drug monitoring?

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Cytochrome P450 2B6 (CYP2B6) participates in the metabolism of important therapeutic drugs such as the nonnucleoside reverse transcriptase inhibitors efavirenz and nevirapine, used in the treatment of HIV infection [1, 2]. There is significant interindividual variability in hepatic expression and catalytic activity of CYP2B6 [3, 4]. Accordingly, the pharmacokinetics of efavirenz is characterized by high interindividual variability in plasma levels [5].

Generally, therapeutic drug monitoring is recommended for drugs with a narrow therapeutic range, whereas pharmacogenetics is aimed at personalizing prescription, which in a perfect world would render therapeutic drug monitoring unnecessary. Both approaches would possibly lead to dose reduction (and drug saving) if many individuals are exposed to supratherapeutic dosing in a given population. These conditions are partially fulfilled for efavirenz. There is a certain ground for dose adjustment by using drug levels, although there is no consensus on the association of pharmacokinetics and efavirenz neuropsychological toxicity [6–8]. However, some individuals that present significant neuropsychological toxicity may benefit from dose reduction [9, 10]. In contrast, there is a good understanding of genetic variation of *CYP2B6* that allows prediction of the pharmacokinetics of efavirenz [11–14]. Thus arises the question as to whether therapeutic drug monitoring or pharmacogenetic prediction should be used to optimize efavirenz therapy. Finally, there would be an interest to use less drug in areas such as Africa, with the goal being less expenditure and the possibility of treating more individuals; however, it would be very difficult to implement therapeutic drug monitoring or pharmacogenetic testing in this continent.

Despite these considerations, it is in the African population that Nyakutira et al. (in this issue) investigate the usefulness of *CYP2B6* genotyping in a population pharmacokinetic model that considers gender and the presence of *CYP2B6*6* as covariates. *CYP2B6*6* is the most common diminished-function allele across human populations. The high allele frequency in blacks (49% in this study), and the fact that 50% of the participants were found to have efavirenz plasma levels above the generally recommended threshold of 4 mg/l, led the authors to propose a priori dose reduction for genetically defined poor metabolizer individuals. Nyakutira et al. propose that poor metabolizer individuals could start efavirenz treatment with a reduced daily dose of 400 mg with the goal of reducing drug use and minimizing toxicity [15].

At population level, prediction could be improved if studies included multiple additional *CYP2B6* alleles associated with diminished metabolic function (http://www.cypalleles.ki.se). We have previously shown that variability in efavirenz plasma levels were better explained by including in the analysis other loss-of-function alleles in addition to *CYP2B6*6* [13]. Considering variants such as the *CYP2B6*16*, **18*, **19*, **20*, **21*, **27*, and **28*, which ae relevant in the African population, would help reduce the 76% unexplained interindividual variability in efavirenz drug levels described by Nyakutira et al [15].

Would genotyping dictate how much drug reduction to effect? Recently, Gatanaga et al. performed a priori dose reduction to 400 mg in four efavirenz-naive individuals homozygous for the *CYP2B6 *6/*6* and one individual with **6/*26*. Despite the preemptive dose reduction, only one individual remained with the 400 mg dose, two individuals required a further decrease to 200 mg/day, and efavirenz

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was discontinued in two patients (in one because of intolerance) [9]. These results emphasize that despite the prediction afforded by *CYP2B6* genotyping, drug monitoring may be needed to assess the outcome of such pharmacogenetic intervention.

Should these proof-of-concept studies prompt a pharmacogenetic-guided trial for efavirenz? The usefulness of a pharmacogenetic-guided treatment strategy has been recently proved by the PREDICT-1 study, where prospective screening for *HLA-B*5701* prior to treatment with abacavir resulted in a significantly lower incidence of hypersensitivity reactions (Mallal et al., *In 4th* International AIDS Conference on HIV Pathogenesis, Treatment and Prevention; *Sydney 2007)*. Conducting such trial may be of limited relevance in the case of efavirenz given the unclear association between drug levels and neuropsychological toxicity, the frequently time-limited nature of efavirenz adverse events, and the rarity of severe toxicity. In addition, if one is to hope for maximal predictability, the study would need to consider multiple *CYP2B6* alleles and possibly genotyping of the accessory metabolic pathways of efavirenz (di Iulio et al., *In 15th Conference on Retroviruses and Opportunistic Infections; Boston 2008*).

A formal prospective controlled clinical trial would be, however, an important step in reconciling pharmacogenetics and therapeutic drug monitoring, a way to understanding the determinants of efavirenz toxicity, and a step toward evaluating the economic value of dose reduction of antiretroviral agents.

References

1. Erickson DA, Mather G, Trager WF, Levy RH, Keirns JJ (1999) Characterization of the in vitro biotransformation of the HIV-1 reverse transcriptase inhibitor nevirapine by human hepatic cytochromes P-450. Drug Metab Dispos 27:1488–1495
2. Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z (2003) The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther 306:287–300
3. Code EL, Crespi CL, Penman BW, Gonzalez FJ, Chang TK, Waxman DJ (1997) Human cytochrome P4502B6: interindividual hepatic expression, substrate specificity, and role in procarcinogen activation. Drug Metab Dispos 25:985–993
4. Lang T, Klein K, Fischer J, Nussler AK, Neuhaus P, Hofmann U, Eichelbaum M, Schwab M, Zanger UM (2001) Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics 11:399–415
5. Csajka C, Marzolini C, Fattinger K, Decosterd LA, Fellay J, Telenti A, Biollaz J, Buclin T (2003) Population pharmacokinetics and effects of efavirenz in patients with human immunodeficiency virus infection. Clin Pharmacol Ther 73:20–30
6. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T (2001) Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 15:71–75
7. Clifford DB, Evans S, Yang Y, Acosta EP, Goodkin K, Tashima K, Simpson D, Dorfman D, Ribaudo H, Gulick RM (2005) Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med 143:714–721
8. Fumaz CR, Munoz-Moreno JA, Molto J, Negredo E, Ferrer MJ, Sirera G, Perez-Alvarez N, Gomez G, Burger D, Clotet B (2005) Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. J Acquir Immune Defic Syndr 38:560–565
9. Gatanaga H, Hayashida T, Tsuchiya K, Yoshino M, Kuwahara T, Tsukada H, Fujimoto K, Sato I, Ueda M, Horiba M, Hamaguchi M, Yamamoto M, Takata N, Kimura A, Koike T, Gejyo F, Matsushita S, Shirasaka T, Kimura S, Oka S (2007) Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 45:1230–1237
10. Hasse B, Gunthard HF, Bleiber G, Krause M (2005) Efavirenz intoxication due to slow hepatic metabolism. Clin Infect Dis 40: e22–e23
11. Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, Clifford DB, Hulgan T, Marzolini C, Acosta EP (2004) Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 18:2391–2400
12. Rotger M, Colombo S, Furrer H, Bleiber G, Buclin T, Lee BL, Keiser O, Biollaz J, Decosterd L, Telenti A (2005) Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 15:1–5
13. Rotger M, Tegude H, Colombo S, Cavassini M, Furrer H, Decosterd L, Blievernicht J, Saussele T, Gunthard HF, Schwab M, Eichelbaum M, Telenti A, Zanger UM (2007) Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther 81:557–566
14. Tsuchiya K, Gatanaga H, Tachikawa N, Teruya K, Kikuchi Y, Yoshino M, Kuwahara T, Shirasaka T, Kimura S, Oka S (2004) Homozygous CYP2B6 *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. Biochem Biophys Res Commun 319:1322–13266
15. Nyakutira C, Röshammar D, Chigutsa E, Chonzi P, Ashton M, Nhachi C, Masimirembwa C (2008) High prevelance of the CYP2B651G → T (*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zinbabwe. Eur J Clin Pharmacol in press